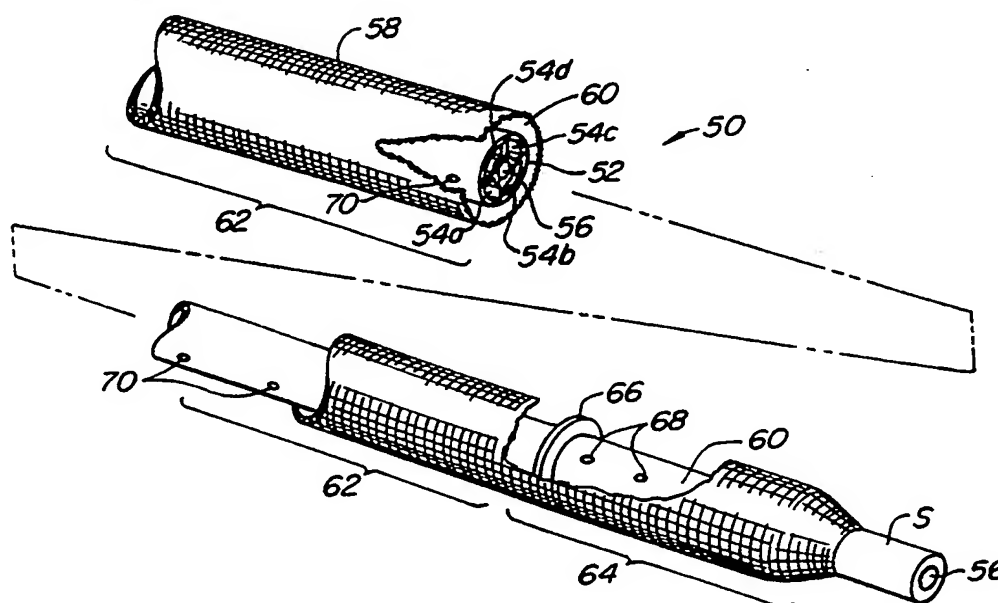




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(54) Title: METHOD AND CATHETER FOR INTRAVASCULAR DRUG DELIVERY

**(57) Abstract**

A vascular perfusion catheter (10) includes a catheter body (12) having a macroporous matrix (40) forming at least a portion of its distal end (16). A solution carrying a desired therapeutic agent may be introduced through the catheter (10) and released through the macroporous matrix (40) under controlled conditions. By forming a matrix as a tubular element (20), the therapeutic agent may be released uniformly in all radial directions over a preselected length within a blood vessel.

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METHOD AND CATHETER FOR INTRAVASCULAR DRUG DELIVERY
BACKGROUND OF THE INVENTION

1. Field of the Invention

5 The present invention relates generally to
apparatus and methods for intravascular drug delivery and
more particularly to a catheter and method for the
controlled infusion of therapeutic agents into an
extended region within a blood vessel over a prolonged
10 time period.

 Catheter infusion of drugs and other active
substances may be useful for treating a wide variety of
disorders. Of particular interest to the present
invention, catheters may be used for the localized
15 administration of thrombolytic agents to dissolve clots
within the vascular system. Typically, the catheter is
percutaneously introduced to the vascular system at the
distal end located adjacent to or within the region of
clot or thrombus. The thrombolytic agent is then
20 delivered through the catheter and released through one
or more discrete perfusion ports formed near the distal
end of the catheter. Alternatively, two or more
catheters may be utilized simultaneously in an attempt to
release the thrombolytic agent throughout the entire
25 clotted region.

 Although generally effective, such catheter
designs suffer from certain disadvantages. In
particular, the use of discrete perfusion ports results
in an uneven distribution of the thrombolytic agent
30 throughout the region being treated, and thrombus
adjacent to each port will receive a much higher
effective concentration of the thrombolytic agent than
received by the thrombus located even a short distance
away. Such an uneven application of the thrombolytic
35 agent increases the chance that the clot will be
fragmented as it is dissolved, exposing the patient to
the release of emboli. Moreover, uneven distribution

requires that the overall delivery rate of the thrombolytic agent be increased so that the entire region of the thrombus may be dissolved. The need to increase the delivery rate is wasteful and results in an increased release of the thrombolytic agent throughout the remainder of the vascular system which can have undesirable side effects. The uneven release of the thrombolytic agent further slows the overall dissolution rate of the thrombus which results in a lengthening of the total time required for each treatment. As the treatment time can frequently be many hours, any increase is highly undesirable. Finally, the use of discrete perfusion ports makes it more difficult to control the release rate which may be as low as several ml/min. Any deviation from the desired release rate can in turn cause the release of excess thrombolytic agent which is wasteful or the release of less than the desired thrombolytic agent which increases the necessary treatment time.

For these reasons, it would be desirable to provide improved apparatus, catheters, and methods for the localized intravascular delivery of therapeutic agents, such as clot dissolving agents. The catheters should be suitable for percutaneous introduction to a desired location within the vascular system, preferably utilizing conventional guide wire introduction techniques. The catheter should further be able to provide highly uniform and controllable delivery rates over an extended axial length thereof so that the therapeutic agent may be released within the vascular system under optimum conditions. It would be further desirable if the catheters were suitable for vascular placement over extended periods of hours.

2. Description of the Background Art

U.S. Patent No. 4,765,339, describes a catheter having a tubular dialysis membrane formed thereon. The catheter is intended primarily for blood analysis, but it

is suggested that it would also be useful for introducing medicaments. It would not, however, be useful for introducing macromolecules as the membrane is macroporous and selected to block proteins and other larger molecules. U.S. Patent No. 4,671,287, describes a catheter having an oxygen permeable bag intended for gastrointestinal oxygenation. U.S. Patent No. 4,274,417, describes a blood gas analysis probe having a permeable tip. U.S. Patent No. 4,318,402, describes a liquid infusion catheter having a perforated outer tube and an unperforated inner tube. U.S. Patent No. 4,717,379, describes a catheter probe having a plurality of radial capillary openings intended for the release of lubricants, washing agents, etc. U.S. Patent No. 4,068,664, describes a surgical suction wand having a perforated tip. U.S. Patent No. 3,528,427, describes a drainage cannula having a perforated tip and an inner tube. U.S. Patent No. 3,593,713, describes an infusion catheter with a perforated (foraminous) rigid shaft. United States Catheter, Inc. has developed a dilatation balloon catheter where the balloon has a plurality of laser-drilled holes which allow release of an inflating medium.

SUMMARY OF THE INVENTION

The present invention comprises an invention and method for the intravascular introduction of therapeutic agents, particularly high molecular weight macromolecular therapeutic agents such as thrombolytic proteins and other polypeptides. The apparatus comprises a catheter having an elongate catheter body with proximal and distal ends. At least one lumen extends axially from the proximal end of the catheter body to a macroporous matrix which is located on the catheter body, typically being at or near the distal end of the catheter body. The macroporous matrix has permeability characteristics which permit the controlled infusion (under a pressure gradient) of macromolecules from the lumen to a region

within a blood vessel which surrounds the matrix. In the specific embodiment, the macroporous matrix has a tubular geometry and forms a portion of the exterior of the catheter body, extending over a desired axial length. In this way, highly uniform and controlled flow of the therapeutic agent can be achieved over extended lengths of the catheter body in a manner which is unattainable with the perforate structures heretofore employed.

In the method of the present invention, the catheter is percutaneously introduced and transluminally positioned so that the macroporous matrix is located within or adjacent to a region within a blood vessel which requires therapy, usually a region of thrombus. A desired therapeutic agent may then be introduced through the lumen, such as a solution containing a thrombolytic polypeptide. Therapeutic agents can be introduced at a concentration and for a time sufficient to achieve the desired therapeutic effect. The controlled and uniform delivery rate of the therapeutic agent can be carefully selected to optimize the treatment conditions.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a perspective view of a controlled perfusion catheter constructed in accordance with the principles of the present invention.

Fig. 2 is a detailed elevational view of the distal end of the catheter of Fig. 1 shown in cross-section.

Fig. 3 is a cross-sectional view taken along line 3-3 of Fig. 2.

Fig. 4 is a cross-sectional view taken along line 4-4 of Fig. 2.

Fig. 5 is a cross-sectional view taken along line 5-5 of Fig. 2.

Fig. 6 illustrates a first alternate embodiment of the catheter of the present invention.

Fig. 7 illustrates a second alternate embodiment of the catheter of the present invention.

Fig. 8 illustrates the method of the present invention using the catheter of Fig. 1 to introduce a thrombolytic polypeptide to a region of thrombus within a patient's vascular system.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is useful for intravascular delivery of a wide variety of therapeutic agents including both low molecular weight drugs, such as antiproliferative drugs, e.g., methotrexate and high molecular weight macromolecules. The invention is particularly useful for the delivery of high molecular weight macromolecular therapeutic agents such as proteins, polypeptides, polysaccharides, mucopolysaccharides, and other biomolecules having a desired therapeutic activity. Specific examples of therapeutic biomolecules include thrombolytic polypeptides, blood thinning agents such as heparin (a mucopolysaccharide), vasodilators, antibodies, immunotoxins, and the like. The present invention is particularly useful when site-specific delivery of a therapeutic agent is required, such as treatment of a solid tumor with an immunotoxin or antiproliferative drug proximate the tumor site, treatment of a stenotic region within the vascular system with a thrombolytic polypeptide, and the like. The following discussion will focus on the treatment of thrombus and plaque within the vascular system using thrombolytic polypeptides, such as tissue plasminogen activator (TPA), streptokinase, urokinase, and the like. The present invention, however, is not limited to such treatment and instead encompasses the delivery of other macromolecules and smaller drugs which may be advantageously released into the vascular system using the catheter and method of the present invention.

The catheter of the present invention comprises an elongate, flexible catheter body having proximal and distal ends. The length and diameter of the catheter

body will vary depending on the intended application, typically having a length in the range from about 60 to 150 cm and a diameter in the range from about 3 to 11 F (one French (F) is equal to 0.33 mm). When the catheter is intended to reach the coronary blood vessels, the catheter body will typically have a length in the range from about 120 to 150 cm and a diameter in the range from about 3 to 8 F. When intended to reach the peripheral blood vessels, the catheter body will usually have a length from about 60 to 150 cm and a diameter from about 3 to 11 F.

The catheter body may include one or more tubular elements with multiple tubes usually being arranged coaxially. The tube(s) will typically be formed by extrusion of an organic polymer, typically a thermoplastic such as nylon, polyurethane, polyethyleneterephthalate (PET), polyvinylchloride (PVC), polyethylene, or the like. The tubes so formed may be reinforced or unreinforced, with reinforcement being optionally provided by metal wires, metal braided cables, or the like. Processes and techniques for forming intravascular catheter bodies are well known in the art and well described in the patent, scientific, and medical literature.

The tube(s) will define one or more lumens extending axially within the catheter body from the proximal end. At least one lumen will be provided for delivering the therapeutic agent from the proximal end of the catheter to near the distal end, as described in more detail hereinafter. Additional lumens may be provided for a variety of purposes, such as to allow introduction and placement of the catheter over a guide wire, and the like. Alternatively, the catheter may employ a fixed guide wire at its distal end to allow for positioning of the catheter within the vascular system.

In a particular embodiment, a lumen will be provided in the distal tip of the catheter to allow a

bypass blood flow through the catheter. Such a bypass blood flow is particularly useful when the catheter is inserted into relatively tight regions of stenosis where blood flow would be otherwise blocked and when the catheter is to be left for extended periods of time. In a second particular embodiment, one or more additional lumens are provided to deliver different therapeutic or other agents to different locations on the catheter. For example, while a thrombolytic agent is being delivered to the distal end of the catheter, a separate lumen might simultaneously deliver an anti-clotting agent along the remaining length of the catheter to inhibit clotting which might otherwise be induced by the catheter.

The catheter of the present invention will include or be attachable to a proximal housing which provides for access to the internal lumen(s) within the catheter body. The proximal housing will include one or more conventional fittings, e.g., luer connectors, which provide for attachment of tubes and introduction of guide wires, as described in more detail hereinafter.

The therapeutic agent delivered by the catheter will be released under a preselected pressure gradient through a macroporous matrix disposed along an axial length of the catheter body, usually although not necessarily disposed near the distal end of the catheter. The macroporous matrix will be in fluid connection with the lumen which carries the therapeutic agent so that the matrix provides a rate-controlling barrier for releasing the therapeutic agent from the catheter. Conveniently, the macroporous matrix will form a portion of the outer surface of the catheter body with the lumen disposed along the entire interior length of the matrix. In this way, the therapeutic agent can perfuse outward through the macroporous matrix to the exterior environment surrounding the catheter in a highly uniform and controlled manner, where the rate of perfusion is controlled both by the characteristics of the matrix and

by the level of internal pressurization as described in more detail hereinafter. It would be possible, of course, to provide additional structure on the catheter to control or direct the flow of therapeutic agent in some manner. In all cases, however, the macroporous matrix will act as a rate controlling element in the delivery system.

In an exemplary embodiment, the macroporous matrix is formed as a close-ended tube or cylinder where the lumen opens into an interior volume within the tube. Such a structure is particularly advantageous since it provides for highly uniform diffusion in all radial directions along the entire length of the macroporous membrane. The length of the macroporous membrane may vary widely, usually being at least 1 cm in length and extending up to the entire catheter length, e.g., 160 cm. Usually, the length of the macroporous matrix will be in the range from about 2 to 50 cm, more usually being in the range from about 2 to 20 cm, and frequently being in the range from 5 to 15 cm.

Alternatively, the macroporous matrix may be formed as a sheath over an internal tubular structure which defines one or more therapeutic agent delivery lumens. Such a structure allows the sheath to be divided into two or more delivery zones where different agents may be simultaneously released from different locations on the catheter. The delivery zones may be axially spaced-apart, radially spaced-apart, or spaced-apart both axially and radially. In a particular embodiment, a first lumen can deliver a therapeutic agent to a macroporous matrix located near the catheter tip while a second lumen delivers an anti-clotting agent, such as heparin, to a macroporous matrix which extends over a portion of or the entire length of the catheter shaft. The ability to inhibit clot formation along the length of the catheter is particularly advantageous when the

catheter is to be left in place for extended periods of time.

5 The macroporous matrix will be formed from a material which is sufficiently porous to allow passage or diffusion of the active molecular species of the therapeutic agent while providing sufficient flow resistance so that the solution containing the therapeutic agent can be released at a desired rate uniformly across the length of the matrix. The material
10 will usually be selected to pass molecules having a molecular weight of at least ten kilodaltons (kD), more usually of at least about 25 kD, preferably of at least about 50 kD, and more preferably of at least about 100 kD. The release rate of the solution which carries
15 the therapeutic agent will depend on a number of factors in addition to the nature of the matrix material, including the delivery pressure, matrix area, matrix thickness, functionalization of the matrix material, and the like. Usually, these characteristics will be
20 selected to provide an overall release rate from the catheter in the range from about 1 cc/hr. to 100 cc/min., usually from about 1cc/min. to 50 cc/min., and more usually in the range from about 5 cc/min. to 25 cc/min.

25 The macroporous matrix will be composed of a biocompatible material, typically being formed from an organic polymer, although in certain cases it may be possible to form the matrix from metals, e.g., stainless steel, or ceramics, e.g., alumina. The macroporous matrix will usually be a single layer of material,
30 although in certain cases it may be desirable to form the matrix as a composite of two or more layers where one layer provides the necessary mechanical strength and another layer provides for the desired molecular weight cutoff and flow resistance. The macroporous matrix may
35 be flexible or rigid, usually being flexible to facilitate manipulation through the vascular system. The matrix material will usually not be substantially

expandable, i.e., it will not dilate substantially in response to internal pressurization, but in some cases may be expandable.

The macroporous matrix may be formed as a woven fabric, non-woven fabric, polymeric film or membrane, or the like. Woven fabrics will typically be formed from organic polymer fibers, such as polyethylene, polypropylene, polyester, nylon, polytetrafluoroethylene (PTFE), polycarbonate, polystyrene, cellulose, polyacetonitrile, and the like. Individual fibers or bundles of fibers (yarns) may be woven into the fabric by conventional techniques, including weaving, braiding, knitting, and the like. The porosity of woven fabrics will be determined primarily by the interstitial spaces between the woven fibers or yarns, with tighter weaves providing a greater flow resistance. Most woven fabrics will have a very high molecular weight cutoff since the interstices in the weave pattern will be large relative to molecular dimensions. The flow resistance, however, will depend primarily on the thickness of the fabric and can be controlled accordingly. Thus, for many applications, the use of woven fabrics as the macroporous matrix material will be preferred. Particularly preferred will be the use of woven polyethyleneterephthalate (PET) fabrics, available under the tradename Dacron®.

Non-woven fabrics, typically spunbonded fabrics, may also find use as the macroporous matrix material. Non-woven fabrics can be prepared from most of the fiber materials listed above with a wide range of porosity and resistance to flow.

The macroporous matrix layers may also be formed from macroporous membranes produced from a wide variety of organic polymers. The preparation of porous membranes having desired characteristics is well described in the technical and patent literature. See, for example, Kirk-Othmer, *Encyclopedia of Chemical*

Technology, 3rd ed., Vol. 15, John Wiley & Sons, New York (1979), pp. 93-131, the disclosure of which is incorporated herein by reference. Exemplary organic membrane materials include polyethylene, polypropylene, polystyrene, nylon, poly(methacrylates), polyvinyl chlorides, and the like.

In some cases, for any of the organic polymers described above, it may be desirable to provide functional groups on the polymeric backbone in order to achieve a desired effect, typically governing the controlled release of the therapeutic agent. For example, hydrophilic or hydrophobic groups might be introduced in order to affect the release rate of therapeutic agents having either hydrophobic or hydrophilic characteristics. Similarly, cationic and/or anionic functionalities may be introduced in order to affect the release of charged therapeutic agents.

It is particularly preferred that the macroporous matrix be "wetable" and capable of retaining a residual volume of therapeutic agent with its structure, such as woven and non-woven fabrics composed of hydrophilic materials, such as polyethyleneterephthalate, and the like. By retaining the therapeutic agent within the matrix, regions within the blood vessel which contact the matrix will be constantly exposed to the agent, even if such contact inhibits active flow through that region. Catheters which employ discrete perfusion ports, in contrast, frequently suffer from blocked ports which can cause a highly uneven release and exposure of therapeutic agent.

Referring now to Figs. 1-5, the construction of a first exemplary catheter 10 constructed in accordance with the principles of the present invention will be described. The catheter 10 comprises a catheter body 12 having a proximal end 14 and a distal end 16. The catheter body 12 includes an inner flexible tubular member 18 and an outer flexible tubular member 20. The

inner flexible tube 18 has a central lumen 22 extending from proximal end 14 to distal end 16, while the inner tube 18 and outer tube 20 together define an annular lumen 24 which also extends from the proximal end to the distal end of the catheter.

A proximal housing 30 is secured to the proximal end 14 of catheter body 12. The housing 30 includes a central port 32 which communicates with the central lumen 22 of the inner flexible tube 18. The housing further includes a side port 34 which communicates with the annular lumen 24. Typically, the central lumen 22 and port 32 will be used to introduce the catheter 10 over a movable guide wire 36 (shown in broken line) in a conventional manner. The side port 34 will be used to introduce a solution carrying the therapeutic agent of interest.

Catheter 10 includes a tubular macroporous matrix 40 formed near the distal end 16. The distal end of tubular macroporous matrix 40 is attached to the outer surface of tubular member 18 in order to close the end of the annular lumen 24. The tubular macroporous matrix forms a continuous surface with the outer flexible tubular member 20 so that, in effect, the catheter body includes a single continuous outer tubular member having a non-porous or impermeable portion and a second porous portion defined by the tubular matrix 40. In this way, the solution carrying the therapeutic agent may be introduced through port 34, travel through the annular lumen 24, and be released under controlled conditions through the macroporous matrix 40.

The length of the tubular macroporous matrix 40 can vary widely within the limits set forth above. The porosity characteristics of the matrix 40 will generally be uniform over the entire surface area so that the release rate of the therapeutic solution will be the same at all locations. It would, of course, be possible to modify the porosity and other characteristics of the

matrix 40 in cases where it is desired to provide a non-uniform release rate of the therapeutic solution.

A second exemplary catheter 50 is illustrated in Fig. 6 and includes an inner flexible tubular member 52 having four isolated axial lumens 54a, b, c, and d extending therethrough. A fifth central lumen 56 is also provided for introducing the catheter 50 over a guide wire (not illustrated) in a conventional manner.

The catheter 50 further includes a tubular macroporous matrix 58 disposed coaxially about the inner flexible tubular member 52 so that an annular lumen 60 remains therebetween. The annular lumen 60 is divided into a proximal region 62 and a distal region 64 by a partition 66 so that the different lumens 54a, b, c, and d may be used to deliver different therapeutic agents to each region. In particular, ports 64 are provided in lumen 54d and lumen 54b (the latter are not visible in Fig. 6) in order to deliver a therapeutic agent to the distal region 64 of the annular lumen 60. From this region, the therapeutic agent is able to infuse in a uniform, controlled manner into the surrounding blood vessel. A second set of ports 70 are provided in lumen 54a and lumen 54c (the latter ports are not visible in Fig. 6) in order to deliver a second therapeutic or other agent to the proximal region 62 of the annular lumen 60. In this way, the second agent can be administered to a different region of the blood vessel simultaneously with the first agent.

The use of multiple delivery lumens and partitions can be extended to form any number of delivery regions along the length of the catheter. The regions may be continuous or separated and may extend over the entire length or only a portion of the length of the catheter. The embodiment illustrated in Fig. 6 will be particularly useful for delivering an anti-clotting agent, such as heparin, along the shaft of the catheter while the desired therapeutic agent is being delivered at

the distal end. The ability to delivery an anti-clotting agent at relatively low controlled rates for extended periods of time is advantageous since catheters can initiate clot formation when present in the vascular system.

Referring now to Fig. 7, the catheter of the present invention can be adapted to allow for bypass blood flow. As illustrated, a catheter 80 may be provided with a plurality of ports 82 which communicate with an internal lumen which allows blood to flow through the catheter. Such a structure is advantageous if the catheter tip is to be inserted into a tight stenotic region where blood flow would otherwise be greatly impeded or blocked entirely. The catheter 80 employs a central lumen 84 to provide the bypass flow path, where the central lumen is open at its distal end 86. Other, separate lumens might also be provided.

Referring now to Fig. 8, use of the therapeutic catheter 10 in treating a region of thrombus T in a patient's superficial femoral artery SF will be described. The guide wire 36 is introduced through the left iliac artery I_L into the right iliac artery I_R and then into the superficial femoral artery SF using an introducer catheter 50 in a conventional manner. The guide wire 36 is positioned so that its distal end passes into the deep femoral artery DF to reach the region of thrombus T. All such positioning steps can be performed under fluoroscopic guidance.

After the guide wire 36 has been properly positioned, the catheter 10 may be introduced by passage over the guide wire until the macroporous membrane 40 lies within the region of thrombus T. A perfusate solution containing the therapeutic agent of interest, typically a thrombolytic polypeptide, is then introduced through port 34 at a rate and for a time sufficient to at least partly dissolve the thrombus T.

The perfusate is typically delivered from a reservoir 100, such as a flexible pouch, through a pump 102 which is connected to inlet port 34 by tubing 104. The pump will typically be capable of delivering a preselected volumetric flow rate over a wide range of pressures. Treatment conditions for two of the most commonly employed thrombolytic agents are as follows.

	<u>Thrombolytic Agent</u>	<u>Volumetric Delivery Rate</u>	<u>Concentration; Preferred Concentration</u>	<u>Treatment Time</u>
10	TPA	5-150cc/hr	60 IU/cc to 10 ⁶ IU/cc; 250,000 to 10 ⁶ IU/cc	1 to 36 hr.
15	Urokinase	5-150cc/hr	0.1 to 25 mg/hr; 5 to 15 mg/hr	1 to 36 hr.

The pressure of the perfusate in the catheter will be determined primarily by the resistance to flow provided by the macroporous membrane 40, and may vary from about 0.1 psi to 500 psi, usually being in the range from about 25 psi to 100 psi. The back pressure on the macroporous membrane 40 provides for highly uniform and controlled release of the thrombolytic agent throughout the region of thrombus T so that dissolution occurs at a constant rate, minimizing the total amount of agent required and reducing the chance that portions of the thrombus will be broken off and released as emboli.

Although the foregoing invention has been described in detail for purposes of clarity of understanding, it will be obvious that certain modifications may be practiced within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A vascular perfusion catheter comprising
an elongate flexible catheter body having a proximal end,
a distal end, and at least one lumen extending axially
therethrough, wherein at least a portion of the catheter
body is formed from a macroporous matrix material which
permits a controlled flow of macromolecules from the
lumen.

2. A vascular perfusion catheter comprising:
an inner flexible tubular member having a
proximal end, a distal end, and a central lumen extending
between the proximal and distal ends; and

an outer flexible tubular member disposed
coaxially about the inner flexible tubular member and
sealed thereto near the distal end to define an annular
lumen having a closed distal end, wherein at least a
portion of the outer flexible tubular member near the
distal end is formed from a macroporous matrix material
which will allow the controlled diffusion of
macromolecules from the annular lumen.

3. A vascular catheter as in claim 2, wherein
the macroporous matrix is disposed at or near the distal
end of the catheter body.

4. A vascular catheter as in claim 3, wherein
the macroporous matrix extends over a length in the range
from about 2 cm to 50 cm.

5. A catheter as in claim 2, wherein the
macroporous matrix has a molecular weight cutoff above
about 10,000 daltons.

6. A catheter as in claim 2, wherein the
macroporous matrix comprises a woven fabric.

7. A catheter as in claim 2, wherein the macroporous matrix comprises a non-woven fabric.

5 8. A catheter as in claim 2, wherein the macroporous matrix comprises an organic polymer membrane.

10 9. A catheter as in claim 2, further comprising means for partitioning the annular lumen into at least two isolated regions and means for separately delivering fluid to each region, wherein the means for partitioning comprises an annular barrier extending between the inner flexible tubular member and the outer flexible tubular member and the means for separately delivering fluids comprises at least two isolated lumens
15 extending from the proximal end of the inner tubular member to the region.

20 10. A catheter as in claim 2, further comprising means for providing a bypass flow through a distal length of the catheter.

25 11. A method for intravascular administration of a macromolecule, said method comprising:
introducing a catheter to a blood vessel; and
administering the macromolecule through a
macroporous matrix disposed on the catheter.

30 12. A method as in claim 11, wherein the macromolecule is a polypeptide.

13. A method as in claim 11, wherein the macromolecule is present in a solution which passes through the macroporous matrix under pressure.

35 14. A method as in claim 13, wherein the pressure is in the range from about 0.1 psi to 500 psi.

15. A method as in claim 13, wherein the flow rate of solution is in the range from about 1 cc/hour to 100 cc/min.

5 16. A method as in claim 11, wherein the macromolecule is a thrombolytic polypeptide.

10 17. A catheter as in claim 11, wherein the macroporous matrix has a molecular weight cutoff above about 10,000 daltons.

18. A catheter as in claim 11, wherein the macroporous matrix comprises a woven fabric.

15 19. A catheter as in claim 11, wherein the macroporous matrix comprises a non-woven fabric.

20 20. A catheter as in claim 11, wherein the macroporous matrix comprises a fabric having of fibers composed of a material selected from the group consisting of polyethylene, polyethyleneterephthalate, polypropylene, polyester, nylon, polytetrafluoroethylene, polycarbonate, polystyrene, cellulose, and polyacetonitrile.

25 21. A catheter as in claim 18, wherein the macroporous matrix comprises a woven polyethylene terephthalate fabric.

30 22. A catheter as in claim 17, wherein the macroporous matrix comprises an organic polymer membrane.

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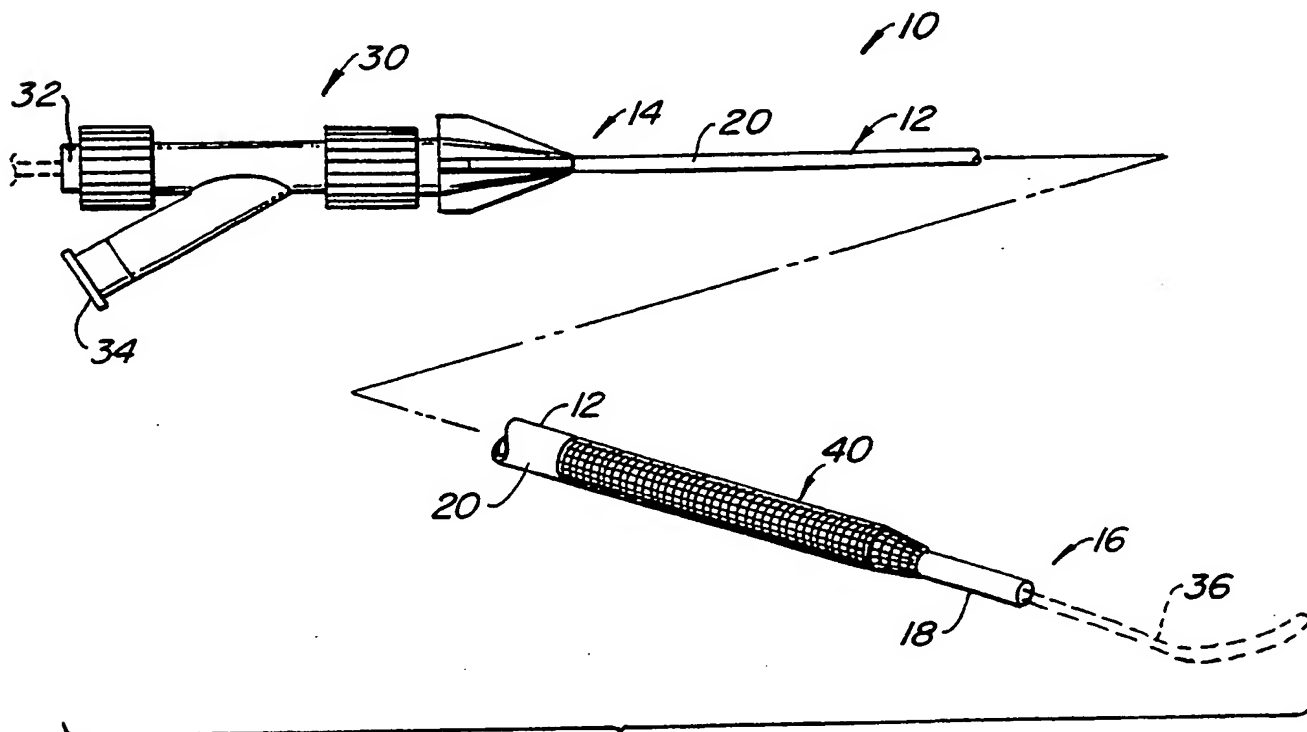


FIG. 1.

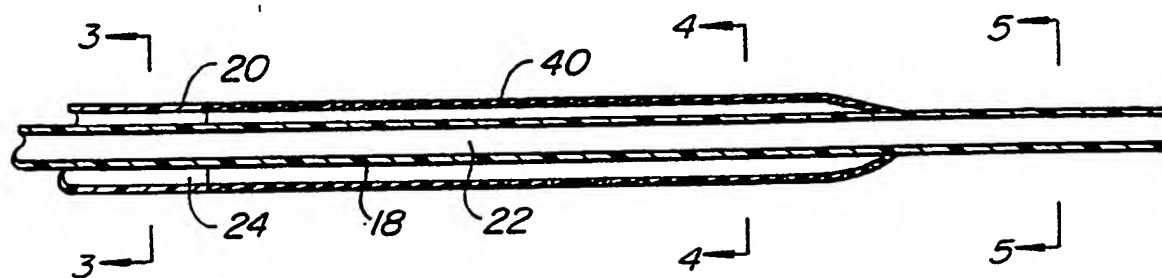


FIG. 2.

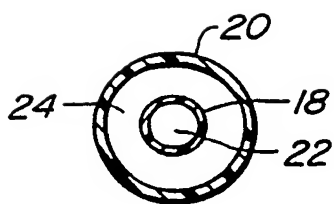


FIG. 3.

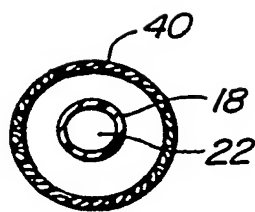


FIG. 4.

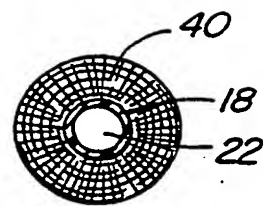


FIG. 5.

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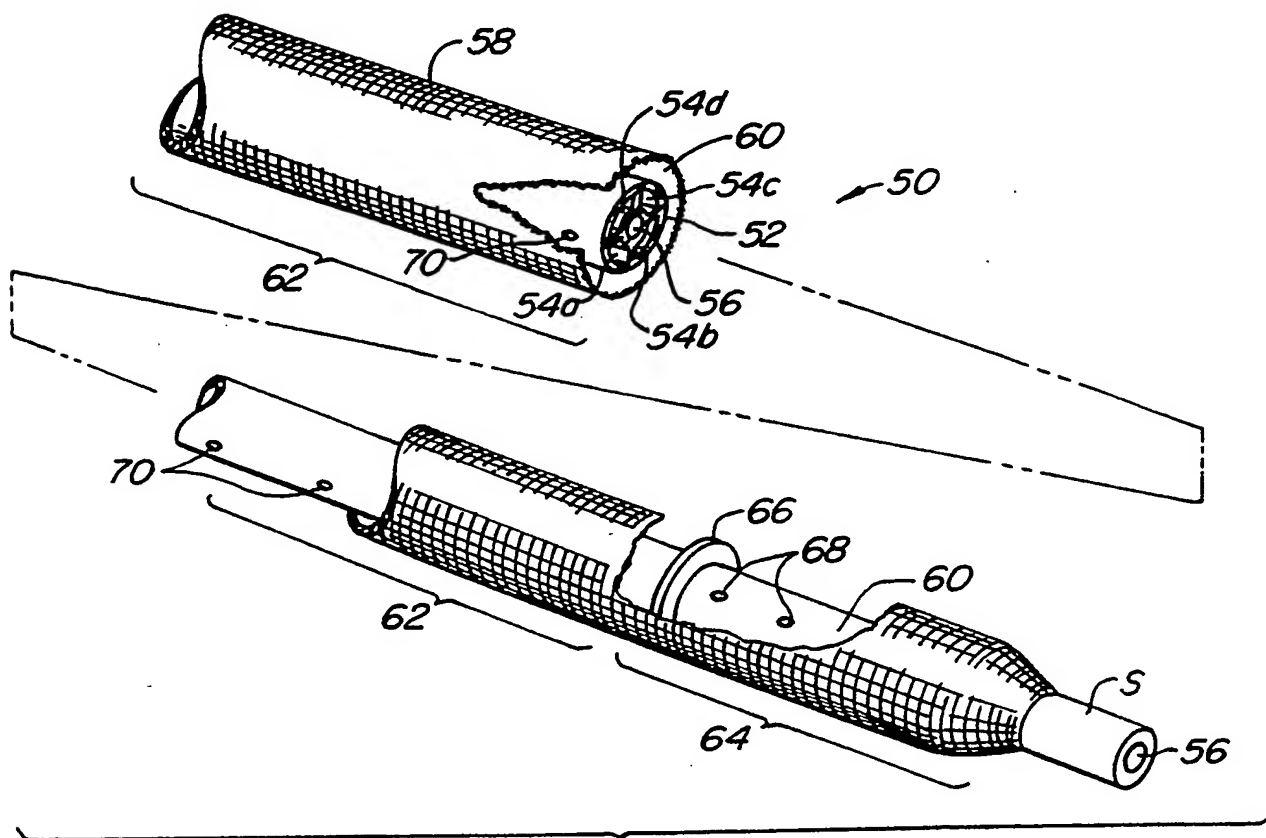


FIG. 6.

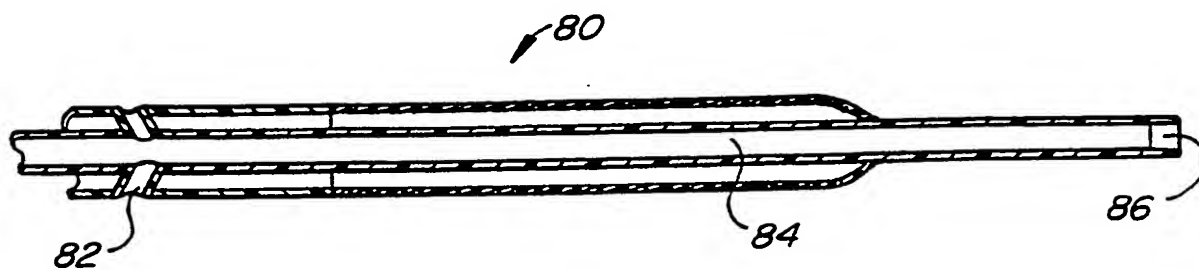


FIG. 7.

SUBSTITUTE SHEET

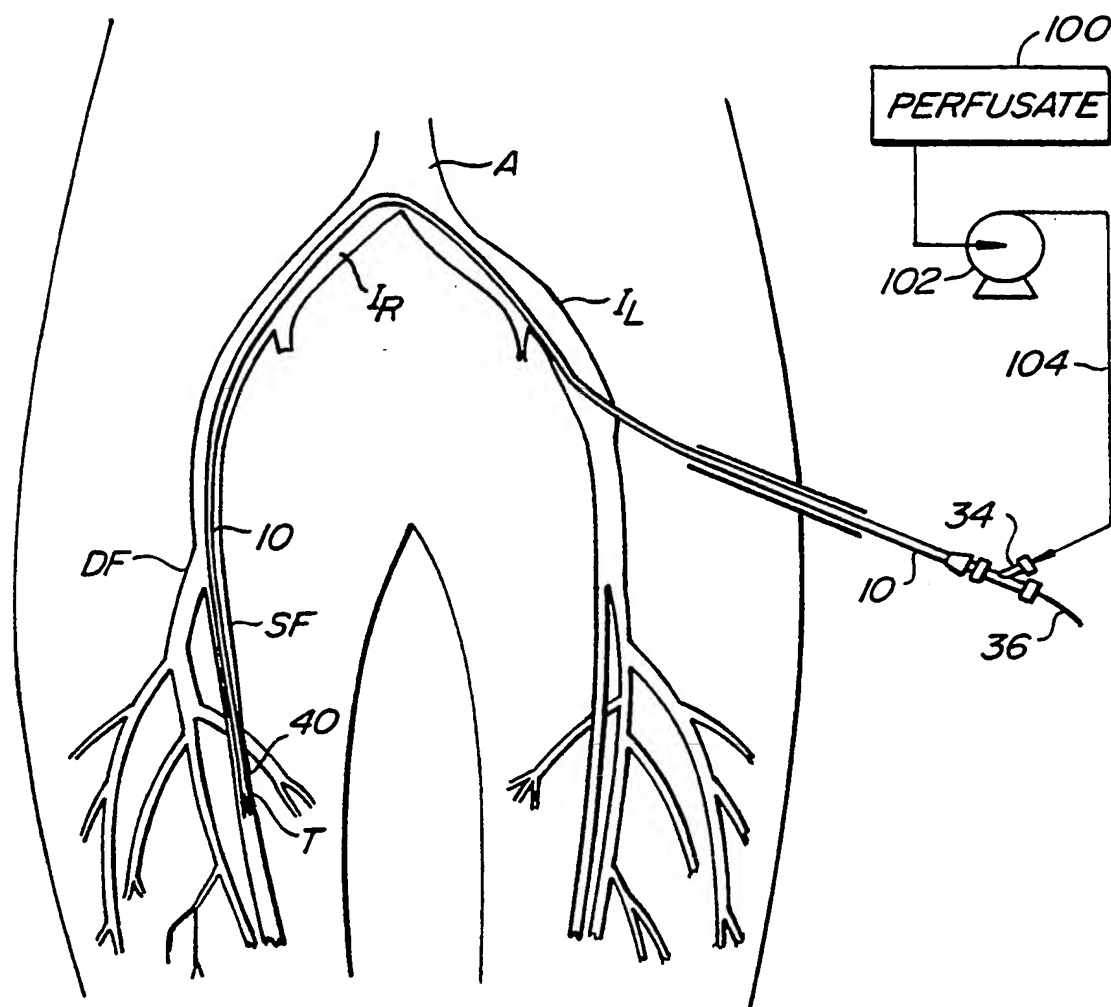


FIG. 8.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/04336

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC(5): A61M 5/00 US Cl.: 604/264,252											
II. FIELDS SEARCHED <div style="text-align: right; margin-right: 100px;">Minimum Documentation Searched ⁷</div> <table style="width: 100%; border: none;"> <tr> <td style="width: 20%; border: none;">Classification System ⁸</td> <td style="border: none;">Classification Symbols</td> </tr> <tr> <td style="border: none; vertical-align: top;">U.S.</td> <td style="border: none; vertical-align: top;">604/96,101,246,252,264,265 ; 128/207.15</td> </tr> </table> <div style="text-align: center; margin-top: 10px;"> Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁹ </div>			Classification System ⁸	Classification Symbols	U.S.	604/96,101,246,252,264,265 ; 128/207.15					
Classification System ⁸	Classification Symbols										
U.S.	604/96,101,246,252,264,265 ; 128/207.15										
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁵ <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%;">Category ¹⁰</th> <th style="width: 70%;">Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²</th> <th style="width: 20%;">Relevant to Claim No. ¹³</th> </tr> </thead> <tbody> <tr> <td style="vertical-align: top;">X, P Y</td> <td style="vertical-align: top;">US, A, 5,021,044 (SHARKAWY) 04 June 1991 See column 1 line 25 to column 4 line 25</td> <td style="vertical-align: top;">1-3,5,8-16 4,6,7</td> </tr> <tr> <td style="vertical-align: top;">Y</td> <td style="vertical-align: top;">US, A, 4,141,379 (MANSKE) 27 February 1979 See column 1 lines 1-8, column 1 line 37 to column 2 line 19, column 3 line 36-61</td> <td style="vertical-align: top;">6,7</td> </tr> </tbody> </table>			Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	X, P Y	US, A, 5,021,044 (SHARKAWY) 04 June 1991 See column 1 line 25 to column 4 line 25	1-3,5,8-16 4,6,7	Y	US, A, 4,141,379 (MANSKE) 27 February 1979 See column 1 lines 1-8, column 1 line 37 to column 2 line 19, column 3 line 36-61	6,7
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Y	US, A, 4,141,379 (MANSKE) 27 February 1979 See column 1 lines 1-8, column 1 line 37 to column 2 line 19, column 3 line 36-61	6,7									
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁰ * Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>											
IV. CERTIFICATION <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; vertical-align: top;"> Date of the Actual Completion of the International Search 07 August 1991 </td> <td style="width: 50%; border: none; vertical-align: top;"> Date of Mailing of this International Search Report <div style="font-size: 1.5em; font-weight: bold; text-align: center;">13 SEP 1991</div> </td> </tr> <tr> <td style="border: none; vertical-align: top;"> International Searching Authority ISA/US </td> <td style="border: none; vertical-align: top;"> Signature of Authorized Officer <i>Nguyen Ngoc Ho</i> Sharon E. Finkel NGUYEN NGOC HO INTERNATIONAL DIVISION </td> </tr> </table>			Date of the Actual Completion of the International Search 07 August 1991	Date of Mailing of this International Search Report <div style="font-size: 1.5em; font-weight: bold; text-align: center;">13 SEP 1991</div>	International Searching Authority ISA/US	Signature of Authorized Officer <i>Nguyen Ngoc Ho</i> Sharon E. Finkel NGUYEN NGOC HO INTERNATIONAL DIVISION					
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FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers _____, because they relate to subject matter ¹² not required to be searched by this Authority, namely:

2. ☒ Claim numbers ¹⁷⁻²² _____, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out ¹³, specifically:

The claims fail to meet the requirements of Article 17(2)(a)(ii) for clarity because they recite an article dependent on a method.

3. ☐ Claim numbers _____, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
☐ No protest accompanied the payment of additional search fees.

